THESIS

ASSOCIATIONS BETWEEN WHITE MATTER MICROSTRUCTURE OF CEREBELLAR CONNECTIONS AND BALANCE PERFORMANCE IN PEOPLE WITH MULTIPLE SCLEROSIS

Submitted by

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ABSTRACT

ASSOCIATIONS BETWEEN WHITE MATTER MICROSTRUCTURE OF CEREBELLAR CONNECTIONS AND BALANCE PERFORMANCE IN PEOPLE WITH MULTIPLE SCLEROSIS

Sensory reweighting, the ability to change the relative contribution of visual, vestibular and proprioceptive systems to balance in response to a changing environment, is critical to balance maintenance. The cerebellum contributes to sensory re-weighting through its white matter connections to the brainstem, the cerebellar peduncles. People with multiple sclerosis (PwMS) have impairments in both sensory reweighting and white matter microstructure of the cerebellar peduncles. The purpose of this study was to examine associations between the white matter microstructure of the cerebellar peduncles and balance performance during sensory-manipulated conditions to elucidate the extent of cerebellar-regulated balance in PwMS. We assessed cerebellar peduncle white matter microstructure with radial diffusivity and fractional anisotropy and standing balance performance with center of pressure-derived measures of path length, sway velocity and root mean square of sway during each sensory-manipulated condition of the Clinical Test of Sensory Integration on Balance in 24 PwMS and 21 neurotypical participants (HC). PwMS exhibited worse balance performance across all sensory-manipulated conditions and worse cerebellar peduncle white matter microstructure compared to HC. Notably, PwMS displayed differentially worse vestibular-based balance performance than HC which was associated with worse cerebellar peduncle white matter microstructure. In addition, PwMS demonstrated unique associations between cerebellar peduncle white matter microstructure and visual-based and proprioceptive-based balance performance that were not found in HC. Our findings suggest that PwMS may place a greater reliance on cerebellar-regulated proprioceptive- and visual-based balance control and demonstrate worse vestibular-based

balance than HC, augmenting previous work indicating abnormal vestibular-based balance and a contribution of the ICP to proprioceptive-based balance performance in PwMS.

ACKNOWLEDGEMENTS

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1. INTRODUCTION

Multiple Sclerosis (MS) is a chronic neurological disease affecting the central nervous system (CNS) characterized by both demyelination and axonal loss (Trapp & Nave, 2008) and is the most common non-traumatic cause of disability in young adults globally (Cameron, M, Nilsagard, 2018; Zwibel, 2009). It is estimated that there are 1 million people living with MS (PwMS) in the United States (Wallin, MD; Culpepper, WJ et al., 2019). These impairments are detectable early in disease progression (Cameron, M, Nilsagard, 2018; Kalron & Achiron, 2013) even when clinically assessed disability is negligible (Cameron et al., 2008; Fjeldstad et al., 2011) or absent (C. L. Martin et al., 2006). Nearly two-thirds of PwMS report lack of postural control as the main symptom contributing to decreased mobility in daily living (Denommé et al., 2014; Jackson, RT, Epstein CM, De l'Aune WR, 1995; Williams NP, Roland PS, Yellin W 1997) an impairment ranked of highest priority among factors affecting quality of life (Salmen et al., 2018).

Postural control is a complex motor skill that involves the dynamic interaction of sensorimotor and biomechanical processes to achieve postural orientation and equilibrium (Shin et al., 2011). Postural orientation entails positioning body segments with respect to sensory reference frames, such as gravity and the visual environment (Diener, Dichgans, Hljlser, et al., 1984; F. B. Horak et al., 2017) Postural equilibrium involves utilizing sensorimotor strategies to maintain balance, the act of maintaining the body's center of mass within its base of support (Pollock, A; Durward, BR et al. 2000; Bronstein, Pavlou, 2013). To maintain balance while standing, humans perform small, continuous corrections to their upright body position called postural sway (F. Horak, 2009; Prieto et al., 1996). Postural sway during stance can be quantified with center-of-pressure (CoP) displacement, which represents the trajectory of the center of mass and the ground reaction

forces applied by the body to maintain balance (Patla et al., 1992). The 1) integration and 2) weighting of sensory information from the visual, vestibular, and proprioceptive sensory systems are two processes of the upmost importance in the maintenance of standing balance (F. B. Horak et al., 1990), numerous studies have shown that perturbation of visual (Peterka, 2002; Lee, D. N., & Lishman, J. R. 1975), vestibular (Day & Cole, 1997; Hlavacka, 1986; Johansson et al., 1995; Nashner, Lewis M., Wolfson, 1974) or proprioceptive (Allum et al., 1998; Jeka, 1997; Johansson et al., 1995; Kavounoudias et al., 1999) systems induce increased postural sway. Thus, to maintain standing balance during changes in environmental conditions, the postural control system must compensate for loss of orientation information from one or more sensory system by adjusting each system's relative contribution to balance in a process called sensory re-weighting (Assländer & Peterka, 2016; F. B. Horak et al., 2017; Horak & Macpherson,1996). For example, when visual feedback is removed while standing on a firm surface, feedback from proprioceptive and vestibular systems is relied upon to a greater degree to maintain balance (Adamcova & Hlavacka, 2007; Terrier & Reynard, 2015; Zhang & Deshpande, 2016). Clinically, the relative contribution of each sensory system to balance while standing is examined by systematically removing one or more sensory input and assessing balance performance when relying on the remaining system(s) (visual-, vestibular- and proprioceptive-based balance performance) in a valid and clinically meaningful assessment called the Clinical Test of Sensory Integration for Balance (Freeman et al., 2018; Shumway-Cook and Horak, 1986). Balance performance in each sensory-manipulated condition is substantially influenced by the cerebellum, a primary neural region involved in controlling the sensorimotor regulation of standing balance (F. B. Horak & Diener, 1994; MacKinnon, 2018; Morton & Bastian, 2004).

The cerebellum is critically involved in sensory integration and re-weighting by functioning as a convergence point for sensory information and an effector of multiple motor areas within the brainstem, midbrain and cortex (Armstrong, 1986; Markwalter et al., 2019; Morton et al., 2004; Shik & Orlovsky, 1976; Takakusaki, 2017). Proprioceptive information from the lower limbs and vestibular information from the vestibular apparatus project through the inferior cerebellar peduncle (ICP) (Armstrong, 1986; Arshavsky et al., 1972; Matsushita et al., 1979; Morton & Bastian, 2006) while visual information from cortical areas projects through the middle cerebellar peduncle (MCP) (Coffman et al., 2011; Markwalter et al., 2019; Rochefort et al., 2013; Shaikh et al., 2005; Vaillancourt et al., 2006). The majority of the superior cerebellar peduncle (SCP) is comprised of fibers projecting from the deep cerebellar nuclei to the brainstem and thalamus to influence descending motor pathways (Habas & Cabanis, 2007; Haines & Mihailoff, 2017; Latash, 2010; Salmi et al., 2010). Accordingly, damage to the cerebellum and its connections are associated with substantial balance impairments while standing such as increased postural sway (Dichgans, 1985; Diener, Dichgans, Bacher, et al., 1984; Mauritz et al., 1979), slow tilts away from upright posture (Marsden, 2018; Scholz et al., 1986; Takakusaki, 2017), ataxia (Diener, Dichgans, Bacher, et al., 1984; Schwabova et al., 2012) and hypermetric postural responses to perturbations (F. B. Horak et al., 1994). PwMS have degraded white matter microstructure of the cerebellar peduncles (Gera et al., 2019; Preziosa et al., 2014; Prosperini, Sbardella, et al., 2013) even in the absence of lesions (De Santis et al., 2019; Massimo Filippi et al., 2003; Hannoun et al., 2018), which is thought to contribute to impairments in sensory integration and re-weighting (Gera et al., 2019; Prosperini, Sbardella, et al., 2013; Prosperini & Castelli, 2018). Behaviorally, PwMS exhibit increased postural sway (Cattaneo & Jonsdottir, 2009; Chung et al., 2008; Daley & Swank, 1981; Fling et al., 2014; Van Emmerik et al., 2010), increased variability of sway (Anbarian et al., 2015; Chung et al., 2008; Denommé et al., 2014; Shin et al., 2011)and increased velocity of sway (Cattaneo et al., 2012; Fjeldstad et al., 2011; Negahban et al., 2013;

Sosnoff et al., 2010) during standing balance. Furthermore, these balance outcomes disproportionately increase when visual input is removed (Denommé et al., 2014; Huisinga et al., 2012; Kanekar & Aruin, 2013; Negahban et al., 2011; Prosperini, Sbardella, et al., 2013; Yahia et al., 2011) or while standing on a compliant surface (Cattaneo et al., 2014; Kanekar et al., 2013; Solomon et al., 2015; Wolfsegger et al., 2013), indicating a decrease in balance performance when one or more sensory system is manipulated. Structural impairments in the connections enabling cerebellar regulation of sensory integration and re-weighting, along with deficits in balance maintenance in different sensory environments identify the cerebellar peduncles as probable contributors to standing balance deficits in PwMS.

Understanding the neural correlates of balance impairment in PwMS is imperative to the development of effective, evidence-based rehabilitative interventions. Recent work found significant associations between cerebellar peduncle microstructure and postural sway in PwMS standing on a firm surface with eyes open (Prosperini, Sbardella, et al., 2013) and with eyes closed (Gera et al., 2019), suggesting that when all sensory inputs are utilized and when primarily proprioceptive inputs are utilized (proprioceptive-based balance), balance performance is related to white matter quality of the cerebellar peduncles. The relationship between cerebellar peduncle microstructure and visual- and vestibular-based balance performance is unknown in PwMS. The purpose of the current study was to examine associations between the white matter microstructural integrity of the inferior, middle and superior cerebellar peduncles and balance performance during visual, vestibular and proprioceptive-based balance tasks. We hypothesized that PwMS would have worse cerebellar peduncle microstructural integrity, worse balance performance in all sensory-manipulated conditions and that ICP microstructure would relate to proprioceptive- and vestibular-based balance performance, MCP microstructure would relate to

visual-based balance performance and SCP microstructure would relate to balance performance in all conditions.

2. METHODS

2.1 Participants

Twenty-four participants with neurologist-confirmed diagnosis of relapsing-remitting MS (RRMS) (17 female, 7 male) and twenty-one neurotypical participants (HC) (16 female, 5 male) were recruited to participate in this study. Participants were excluded if they had an ongoing MS relapse, other neurologic conditions besides MS, significant vision impairments, vestibular injuries that would impact balance (i.e. vertigo), concurrent conditions affecting ability to comply with the study procedures including musculoskeletal injury or were unable to abstain from medications that might impair their balance in the 24 hour time period prior to testing. Eligible participants were between 18 and 85 years of age, scored a 4.0 or less on the Expanded Disability Status Scale (EDSS), could stand or walk unassisted on a firm surface for at least 30 minutes. Approval for this study was given by the local Institutional Review Board at Colorado State University and all participants provided written informed consent prior to participation.

2.2 Procedures

2.2.1 Balance Assessment

Balance was assessed by the instrumented Clinical Test of Sensory Integration for Balance (iCTSIB), a valid and clinically-meaningful measure of sensory organization (Cohen et al., 2014; Freeman et al., 2018). Participants performed following four conditions in the clinically designed order: rigid surface, eyes open (C1); rigid surface, eyes closed (C2); compliant surface, eyes open (C3); compliant surface, eyes closed (C4) with their feet together and hands on hips while focusing their vision on a fixed target during eyes open conditions and standing on a foam, 7 cm thick Elite Balance pad (Airex, Sins, Switzerland) during compliant surface conditions (Fig. 1).

Participants performed each condition for one, 30 second trial while standing on a BTracKS balance plate (BBP) (BalanceTracking Systems, Inc., San Diego, CA). The BBP was chosen to derive CoP-based metrics of postural sway because it is a cost-effective, portable, and valid alternative to laboratory-grade force plates (O'Connor et al., 2016; Richmond et al., 2018).

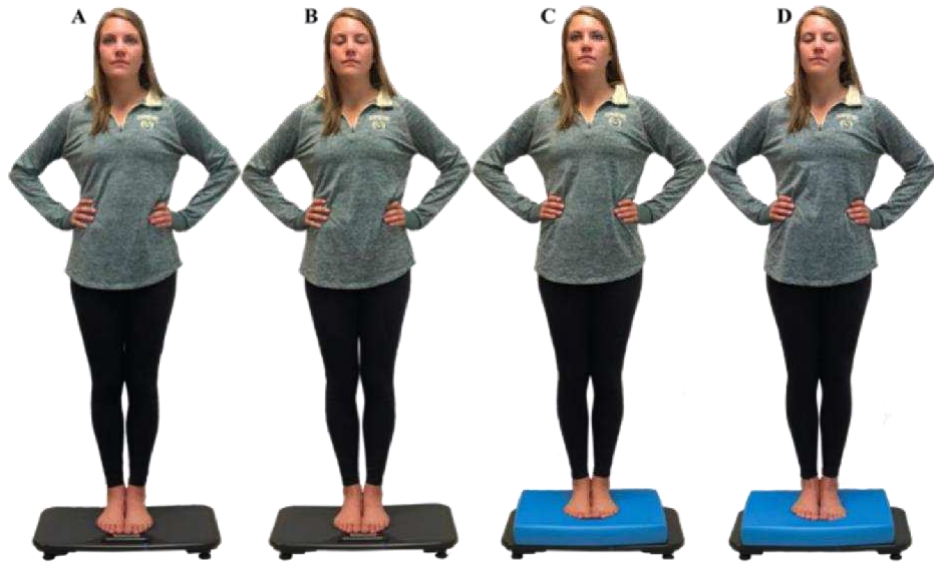

Figure 1. iCTSIB conditions performed on a BTrackS balance plate: rigid surface, eyes open (A); rigid surface, eyes closed (B); compliant surface, eyes open (C); compliant surface, eyes closed (D).

2.2.2 Analysis of Balance Performance

For each trial, the BBP collected ground reaction forces at 25 Hz and data was filtered with a second order, low-pass Butterworth filter with a cutoff frequency of 4 Hz using Balance Tracking Systems Inc. software. CoP-derived data was exported from the BBP for further analysis using custom MATLAB (MathWorks, Natick, MA, version R2018b) scripts (Richmond et al., 2018) derived from equations originated by Thomas Prieto and colleagues (Prieto et al., 1996).

2.2.3 MRI Data Acquisition

On the same day, prior to postural assessments, diffusion weighted images were acquired with a 3.0 T Siemens MAGNETOM Prisma (Siemens Medical Solutions USA, Inc., Malvern, PA) MRI scanner equipped with a 32-channel head coil. Diffusion weighting occurred anterior to posterior in 27 directions (b-value = 2400 s/mm2); six images were unweighted (b=0 s/mm2). An echo planar imaging sequence was utilized (repetition time (TR) = 4000 ms, echo time (TE) = 77.0 ms, field of view read = 224 mm (224 mm (RL), 216 mm (AP), 144 mm (FH), 72 (transversal) slices, slice thickness = 2.00 mm, voxel dimensions = 2.0 x 2.0 x 2.0 mm) for the diffusion weighted image acquisition that was 13 minutes in scan time. One high-resolution T1-weighted MP-RAGE sequence (resolution = 0.8 x 0.8 x0.8 mm, a field of view read = 356 mm (180 mm (RL), 256 mm (AP, 256 mm (FH)), slice thickness = 0.8 mm, echo time (TE) = 2.07 ms , repetition time (TR) = 2400 ms, number of slices = 224 (sagittal)) was acquired for post-processing registration with a total scan time of 36 minutes.

2.2.4 DTI Processing

The microstructural quality of the cerebellar peduncles was assessed during post processing analysis with ExploreDTI software (www.exploredti.com) (Leemans et al. 2008). Raw images underwent visual inspection to detect motion artifact and image data was corrected for signal drift, Gibbs ringing, eddy currents, subject motion and distortions using tools within ExploreDTI. High resolution T1 images from each participant were used for alignment purposes while using eddy current and subject motion corrective applications. The International Consortium of Brain Mapping (ICBM) DTI-81 atlas was applied to the normalized images and the outcome measures of fractional anisotropy (FA) and radial diffusivity (RD) were averaged across the 3D SCP, MCP, ICP labels for each participant. FA is a rotationally invariant, normalized measure that quantifies anisotropy of the diffusion tensor in a range of 0 to 1, with higher values indicating better overall

tract quality (Van Hecke et al., 2016). Radial diffusivity is a measure of diffusion perpendicular to the principal direction of diffusion and is considered an indirect marker of neural myelination (Gulani et al., 2001).

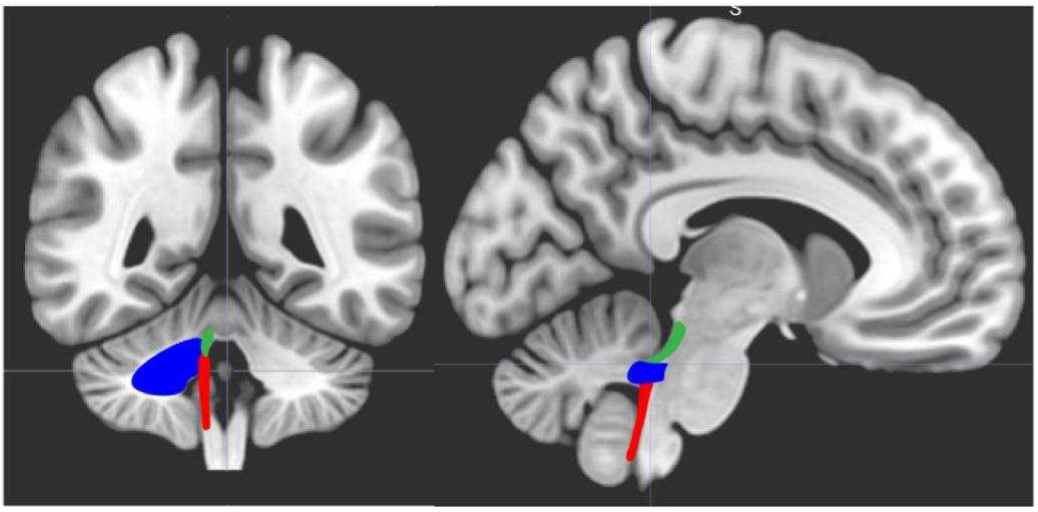

Figure 2. Depiction of the Inferior Cerebellar Peduncle (ICP, red), Middle Cerebellar Peduncle (MCP. blue), Superior Cerebellar Peduncle (SCP, green) from the ICBM DTI-81 Atlas.

3. STATISTICAL ANALYSIS

All statistical analyses were carried out using R (RStudio Team, 2018). P-values ≤ 0.05 were considered statistically significant. We performed a 2x4 (group x condition) repeated measures analysis of variance (RMANOVA) for CoP-derived measures of path length, velocity, and root mean square of sway (RMS) collected during the iCTSIB. Significant main effects were investigated with post hoc analyses and Bonferroni-corrected for multiple comparisons. Paired ttests of each pair of tracts showed no significant differences between the right and left hemispheres (all $p>0.5$), therefore, bilateral averages of each of the three tracts were used. Microstructural integrity of fiber tracts comprising the cerebellar peduncles were compared between groups using a 2x3 (group x structure) RMANOVA to test the hypothesis that PwMS have worse microstructural integrity of the cerebellar peduncles. Significant main effects were further analyzed with post hoc analyses and Bonferroni-corrected for multiple comparisons. To assess associations between cerebellar peduncle microstructure and balance performance (assessed by path length, velocity, and RMS) in each iCTSIB condition, Spearman's correlations were performed after a Shapiro-Wilks test revealed the data were not normally distributed. Three PwMS and one HC were unable to complete C4 and one PwMS was unable to complete C3; thus, their data are not included for those balance conditions. Data are reported as mean ± standard deviation (SD) unless otherwise noted.

4. RESULTS

4.1 Characteristics

Participant characteristics are shown in Table 1. Groups were well matched in age, hours of physical activity completed per week and sex; however, PwMS had a significantly greater BMI than HC ($p<0.05$) (Table 1.).

Table 1. Participant characteristics: demographic, anthropometric, hours physical activity information and MS severity. Values are mean (standard error); h/week = hours per week.

Characteristics	HC (n=21)	PwMS (n=24)	p value
Age (years)	46.3 (10.11)	49.2 (10.04)	0.51
Sex (F, M)	16, 5	17, 7	0.69
BMI (kg/m^2)	23.6 (5.15)	26.6 (5.43)	0.01
Physical activity (h/wk)	3.87 (0.83)	4.25 (0.87)	0.71
EDSS	N/A	3.07(0.63)	

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4.2 Balance

The iCTSIB displayed a significant main effect of group for path length ($F_{1,3} = 6.29$; $p<0.05$), velocity ($F_{1,3} = 6.38$; $p<0.05$) and RMS ($F_{1,3} = 5.41$; $p<0.05$) such that PwMS exhibited significantly greater path length, velocity and RMS than HC, reflective of worse balance performance (Table 2.). We also detected a significant main effect of condition for path length ($F_{1,3} = 213.47$; $p<0.0001$), velocity ($F_{1,3} = 213.08$; $p<0.0001$) and RMS ($F_{1,3} = 99.22$; $p<0.0001$) that revealed a significant increase in values as the iCTSIB systematically removed input from sensory systems and thus progressively increased the difficulty of each condition. Specifically, path length, velocity and RMS were significantly greater in C4 than in all other conditions ($p<0.0001$ for all), significantly greater in C3 than in C1 (path length: $p<0.0001$; velocity:

p<0.0001; RMS: p<0.001) and greater in C3 than C2 (path length: p<0.05; velocity: p<0.05), although differences in RMS between C3 and C2 did not reach statistical significance (p>0.05). Finally, path length, velocity and RMS in C2 were greater than in C1, however, differences did not reach statistical significance (p>0.05 for all).

Table 2. Balance variables collected from each iCTSIB condition separated by group. Values are mean ± SD, p values reflect main effect of group.

		HC	PwMS	
Balance variables	Conditions	Mean± SD	Mean± SD	*p* value
Path length (cm)				0.016
	C1	52.64 ± 16.10	70 ± 32.24	
	C2	73.81 ± 24.50	106.94 ± 60.15	
	C3	104.47± 32.99	139.68 ± 55.74	
	C4	206.75 ± 61.82	247.29 ± 92.30	
Velocity (cm/s)				0.015
	C1	1.74 ± 0.53	2.34 ± 1.07	
	C2	2.45 ± 0.81	3.56 ± 2.00	
	C3	3.47 ± 1.09	4.64 ± 0.37	
	C4	6.86 ± 2.05	8.22 ± 3.07	
RMS (cm)				0.025
	C1	0.92 ± 0.24	0.94 ± 0.28	
	C2	1.02 ± 0.33	1.24 ± 0.60	
	C3	1.3 ± 0.34	1.52 ± 0.51	
	C4	2.01±0.55	2.60 ± 0.95	

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In addition, we report a significant group x condition interaction for RMS ($F_{1,3}$ = 4.08; p<0.01). Post hoc analysis revealed that PwMS displayed significantly greater RMS than HC in C4 (p<0.001); differences in RMS for C1, C2 and C3 did not reach statistical significance (p>0.05). Furthermore, RMS was greater in C4 than in C3 (p<0.0001), C2 (p<0.0001), and C1 (p<0.0001) and greater in C3 than in C1 (HC: p<0.05; PwMS: p<0.0001). Differences between C3 and C2 were significant only in PwMS (HC: p>0.05; PwMS: p<0.05) and differences between C1 and C2 were non-significant in either group (HC: p=1.0; PwMS: p>0.05) (Fig. 3).

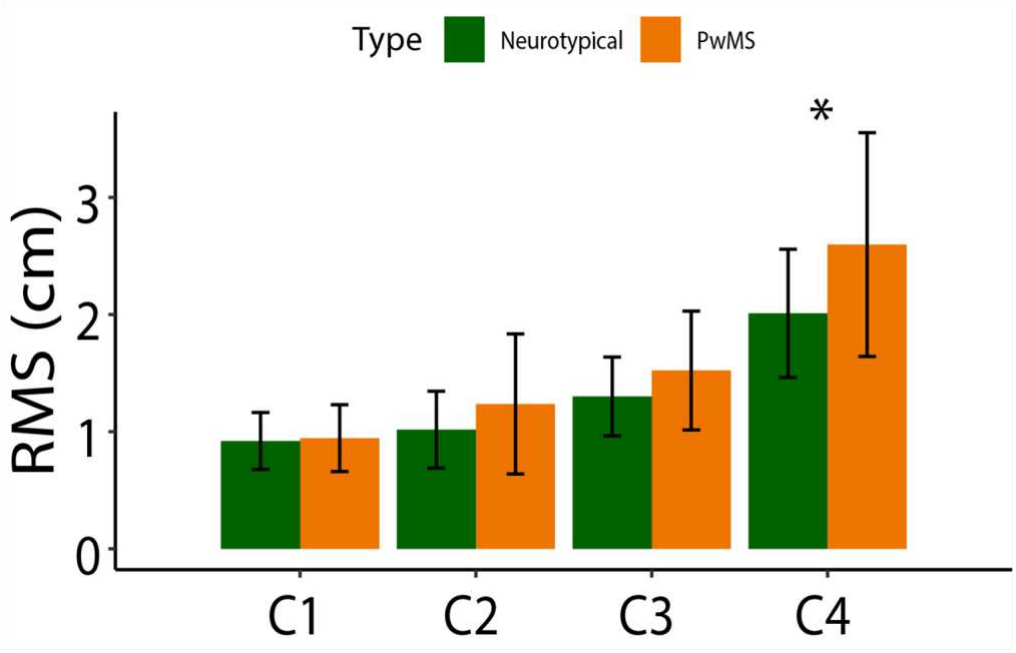

Figure 3. RMS by group and iCTSIB condition indicating a significant difference in RMS between groups in C4. *p<0.001.

4.3 Imaging

We report a significant main effect of group for RD ($F_{1,2} = 8.99$; $p<0.01$) and FA ($F_{1,2} = 8.26$, $p<0.01$) such that PwMS had significantly greater RD and lower FA compared to HC, indicative of worse white matter microstructure (Fig.4). A significant main effect of structure was detected for RD ($F_{1,2} = 6.17$; $p<0.01$) such that MCP RD was greater than SCP RD and ICP RD, SCP RD was greater than ICP RD, although no differences reached statistical significance ($p>0.05$ for all). We found a main effect of structure for FA ($F_{1,2} = 172.62$; $p<0.0001$) where MCP FA was significantly lower than both SCP FA ($p<0.0001$) and ICP FA ($p<0.0001$), ICP FA was significantly lower than SCP FA ($p<0.0001$) to suggest worse microstructure in order of MCP, SCP, ICP. There were no group x structure interactions for RD ($F_{1,2} = 2.38$, $p >0.5$) or FA ($F_{1,2} = 2.94$, $p >0.05$), indicating that PwMS exhibited worse microstructural integrity across all cerebellar peduncles.

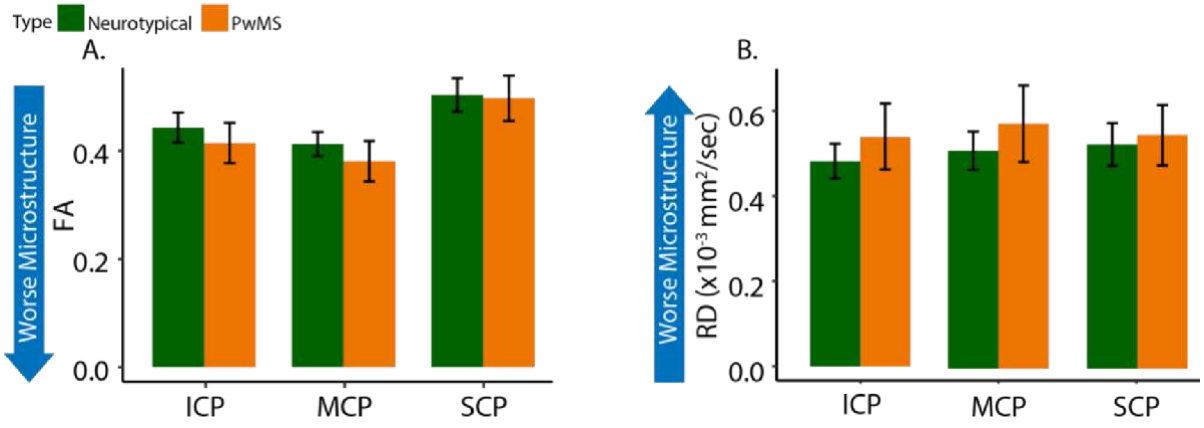

Figure 4. A significant main effect of group ($p<0.01$) for RD (A) and FA (B) indicate that PwMS have greater RD and lower FA for all structures compared to HC. Data are mean ± standard deviation. RD = Radial Diffusivity ($x10^3$ mm^2/s); FA = Fractional Anisotropy.

4.4 Correlations

We found significant negative correlations between FA of the ICP with both path length (rho = -0.48, $p<0.01$), and velocity (rho = -0.48, $p<0.01$) during the proprioceptive-based balance condition (C2) in PwMS**,** but not in HC ($p>0.05$ for all) (Fig.5A, B), demonstrating that worse ICP microstructure (lower FA) is associated with worse proprioceptive-based balance performance in PwMS. Associations between FA of the ICP and RMS did not reach statistical significance in PwMS ($p>0.05$). No significant associations were found between RD of the ICP and path length, velocity or RMS in either group ($p>0.05$) (Table 4.).

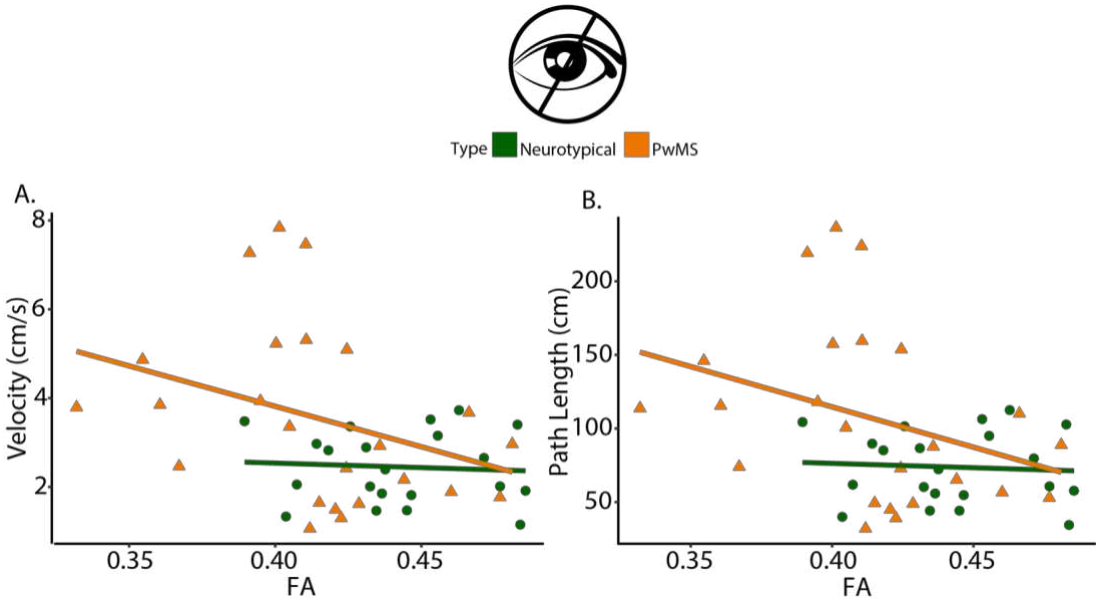

Fig.5. In C2, FA of the ICP is significantly associated with A) path length (HC: rho =-0.07, p>0.05; PwMS: rho = -0.48, p<0.01) and B) velocity (HC: rho =-0.06, p>0.05; PwMS: rho = -0.48, p<0.01) in PwMS.

We report significant correlations between both FA and RD of the MCP with path length (FA: rho= -0.35, p<0.05; RD: rho= 0.39, p<0.05) and velocity (FA: rho = -0.36, p<0.05; RD: rho = 0.40, p<0.05) during the visual-based balance condition (C3) in PwMS, but not in HC (p>0.05 for all). No significant correlations were detected between MCP microstructure and RMS in either group (p>0.05) (Table 3.).

Table 3. Correlation coefficients (rho) between MCP microstructure and visual-based (C3) balance performance. *p<0.05.

		Path length (cm)	Velocity (cm/s)	RMS (cm)
		C3	C3	C3
FA MCP	HC	-0.28	-0.29	0.05
	PwMS	-0.35*	-0.36*	-0.22
RD MCP	HC	0.28	0.28	-0.05
	PwMS	0.39*	0.40*	0.29

Conversely, we found significant correlations between ICP microstructure and vestibular-based balance performance (C4) in both groups. Specifically, FA of the ICP had a significant negative association with RMS in PwMS (rho = -0.40, $p<0.05$; Fig.4) and RD of the ICP displayed significant positive associations with path length (rho = 0.40, $p<0.05$) and velocity (rho = 0.41, $p<0.05$) in HC (Table 4.). These results indicate that higher quality ICP microstructure (i.e. higher FA, lower RD) is associated with increased vestibular-based balance performance in both groups. Non-significant associations were found between FA of the ICP and path length ($p>0.05$), velocity ($p>0.05$) in PwMS and between FA of the ICP and all balance outcomes ($p>0.05$) in HC. Additionally, we report non-significant associations between RD of the ICP and all balance outcomes in PwMS ($p>0.05$) and between RD of the ICP and RMS ($p>0.05$) in HC.

Table 4. Correlation coefficients (rho) between ICP microstructure and proprioceptive- (C2) and vestibular- (C4) based balance performance. *p<0.05, ** p<0.01.

		Path length (cm)		Velocity (cm/s)		RMS (cm)	
		C2	C4	C2	C4	C2	C4
FA ICP	HC	-0.07	-0.30	-0.06	-0.31	-0.06	-0.14
	PwMS	-0.48**	-0.35	-0.48**	-0.34	-0.21	-0.40*
RD ICP	HC	0.18	0.40*	0.19	0.41*	0.16	0.28
	PwMS	0.21	0.29	0.21	0.27	-0.03	0.27

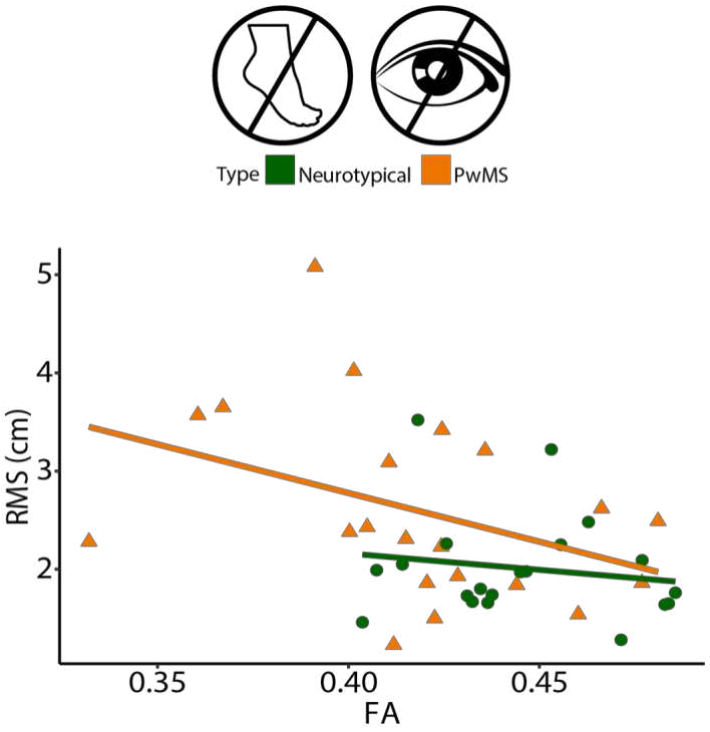

Fig.5.In C4, FA of the ICP and RMS (C) are significantly associated in PwMS (HC: rho= -0.14, p>0.05; PwMS: rho = -0.40; p<0.05).

In summary, we found associations between FA ICP and path length, velocity in C2 in PwMS, demonstrating that the microstructure of the cerebellar peduncle carrying proprioceptive information is related to balance performance in proprioceptive-based balance conditions in PwMS. PwMS also exhibited associations between FA, RD MCP and path length, velocity in C3, indicating that the microstructure of the cerebellar peduncle carrying visual information is related to visual-based balance performance in PwMS. Both HC and PwMS exhibited associations between the microstructure of the cerebellar peduncle carrying vestibular information and vestibular-based balance performance where RD ICP is associated with path length, velocity in C4 in HC and FA ICP is associated with RMS in PwMS.

5. DISCUSSION

To our knowledge, this is the first study to examine the relationship between white matter microstructural integrity of the cerebellar peduncles and visual-, vestibular-based balance performance in PwMS. Consistent with our hypotheses, we report worse cerebellar peduncle white matter microstructure and worse balance performance across all conditions in PwMS compared to HC. In addition, we report a group by condition interaction for RMS such that PwMS displayed significantly higher RMS in C4 than HC, reflective of worse vestibular-based balance performance. Furthermore, PwMS demonstrated associations between ICP microstructure and proprioceptive-based balance performance that were not present in HC. Both groups exhibited associations between MCP microstructure and visual-based balance performance and ICP microstructure and vestibular-based balance performance. Conversely, SCP microstructure was not related to balance performance in any condition. Taken together, these results suggest that PwMS demonstrate differentially worse vestibular-based balance control and are more reliant on cerebellar control of proprioceptive-based balance compared to HC.

5.1 Balance

Standing balance deficits are common in PwMS (Gunn et al., 2015; Mazumder et al., 2014) and can occur early in the disease process (Kalron et al., 2013) even when clinicallydetected disability is minimal (Cameron et al., 2008; Denommé et al., 2014; Fjeldstad et al., 2011; C. L. Martin et al., 2006), and worsen with disease severity (Daley et al., 1981; McLoughlin et al., 2015). Maintaining balance while standing requires the integration of sensory information from the visual, vestibular, and proprioceptive systems along with altering each system's relative

contribution to balance when the availability of sensory information changes. PwMS exhibit impaired standing balance when information from all sensory systems is available (firm surface, eyes open) (Cattaneo et al., 2009; Chung et al., 2008; Fling et al., 2014; Gera et al., 2019; Huisinga et al., 2012; Kanekar et al., 2013; Prosperini, Fortuna, et al., 2013; Prosperini, Sbardella, et al., 2013) and worse balance than neurotypical adults when vision (Gera et al., 2019; Prosperini, Fortuna, et al., 2013)(Daley et al., 1981; Huisinga et al., 2012) or reliable proprioceptive feedback is removed (Cattaneo et al., 2009; Fjeldstad et al., 2011; Fling et al., 2014; Kanekar et al., 2013). Our results echo these findings; PwMS demonstrated greater path length, velocity and RMS than HC, suggesting impairments in both the integration of sensory information when all sensory inputs are available and the appropriate reweighting of each system's contribution to balance when vision or reliable proprioceptive feedback is removed.

While we had a main effect of condition such that balance performance decreased as accurate sensory input was systematically eliminated, of more interest is the group by condition interaction we observed for RMS in C4. Specifically, PwMS had significantly greater RMS in C4, indicating that PwMS have worse vestibular-based balance performance than HC. This is in agreement with literature that found that the highest percentage of abnormal path length values (above 2 SD of age-matched HC values) in PwMS occurred while balancing with their eyes closed on a foam surface (Cattaneo et al., 2009) and that PwMS exhibited significantly greater sway velocity than HC solely in the eyes closed, foam surface condition (Fjeldstad et al., 2011). Similarly, Negahban and colleagues detected significantly greater velocity, sway area and variability of anterior-posterior (AP) velocity in PwMS in the eyes closed, foam surface condition than HC (Negahban et al., 2011).

Moreover, vestibular function is impaired in up to 85% of PwMS (Cohen et al., 2014; RaeGrant et al., 1999; Versino et al., 2002; Zeigelboim et al., 2008) and is found to substantially influence balance performance. Recent work found significant improvements in standing balance performance in PwMS who underwent 6 weeks of vestibular system-specific balance training compared to those who underwent aerobic exercise and stretching (Hebert et al., 2011) or those who did not undergo any intervention (Hebert et al., 2018). Interestingly, our detection of worse vestibular-based balance in PwMS was demonstrated by a significant increase solely in RMS. RMS has been shown to be reflective of vestibular-based balance performance in previous work demonstrating significantly higher RMS values in patients with paroxysmal positional vertigo and diabetic peripheral neuropathy compared with diabetic peripheral neuropathy alone, indicating that patients with vestibular impairment have higher RMS than patients with proprioceptive impairment alone (D'Silva et al., 2017). Additionally, the use of a vestibulocochlear implant with head-referenced spatial information in children with bilateral cochleovestibular loss significantly reduced RMS, demonstrating a subsequent improvement in balance after augmenting vestibular function (Wolter N 2019). In PwMS, deficits in visual, vestibular and proprioceptive-based balance performance are thought to be induced by structural impairments in white matter tracts connecting posturerelated brain regions (Cameron & Lord, 2010; Doty et al., 2018; Fling et al., 2014; Gera et al., 2019; Kolasa et al., 2019; Prosperini et al., 2011; Prosperini, Fortuna, et al., 2013). Impairments in white matter microstructural integrity have been detected even in the earliest clinical stages of MS (De Santis et al., 2019; Massimo Filippi et al., 2003), largely independent of MRI-visible lesions (Allen et al., 2001; Haight et al., 2018; Hannoun et al., 2018; Rovaris & Filippi, 2007; Werring et al., 1999), and are found throughout the CNS (Bammer et al.,

2000; Ciccarelli et al., 2003; M Filippi et al., 2001; Prosperini, Sbardella, et al., 2013; Prosperini et al., 2014).

5.2 Imaging

Of importance to standing balance performance, we detected significantly higher RD and lower FA in the cerebellar peduncles in PwMS compared to HC. Our findings are largely in agreement with current literature demonstrating greater RD and lower FA of the cerebellar peduncles in PwMS compared to HC (Gera et al., 2019; Hannoun et al., 2018; Preziosa et al., 2014; Prosperini, Sbardella, et al., 2013; Prosperini et al., 2014). In contrast, Anderson and colleagues did not detect significant differences in cerebellar peduncle white matter microstructure between PwMS and HC (Anderson et al., 2011), likely due to their limited spatial resolution decreasing the fidelity of their DTI parameters (Polders et al., 2011; Van Hecke et al., 2016). In an MS group comprised primarily of RRMS participants, Gera and colleagues found significant differences in RD solely in the ICP and SCP and not in the MCP and no significant differences in FA of any cerebellar peduncle in PwMS compared to HC (Gera et al., 2019). Similarly, Hannoun and colleagues found no significant differences in RD of the MCP or FA of any cerebellar peduncle when comparing RRMS participants to HC, despite detecting significantly worse RD and FA of all cerebellar peduncles in an MS group comprised of different MS subtypes (Hannoun et al., 2018). These mixed results highlight the well-established heterogeneity in the degree of balance deficits expressed by PwMS (Abdel-Aziz et al., 2015; Beer et al., 2012; Cameron et al., 2010; Comber et al., 2018; Frzovic et al., 2000; Huisinga et al., 2014; Prosperini et al., 2018), as the pathogenesis of this disease is complex and not fully understood (Massimo Filippi & Rocca, 2005; Frischer et al., 2009; Lassmann et al., 2001; Lucchinetti et al., 2000; Noseworthy et al.,

2000; Trapp et al., 2008). Poor microstructural integrity of the cerebellar peduncles diminishes cerebellarregulated sensory integration and re-weighting (Gera et al., 2019; Prosperini, Sbardella, et al., 2013); likely reducing standing balance performance in PwMS.

5.3 Correlations

We found significant associations between ICP FA and proprioceptive-based balance performance in PwMS that were not present in HC, suggesting that PwMS have a comparatively greater reliance on cerebellar-regulated proprioceptive balance control. Proprioceptive information from the lower limb ascends the spinal cord in the posterior spinocerebellar tract, projects through the ICP and reaches the fastigial nucleus in the vermis, which sends projections to the brainstem and modifies the output of upper motor neuron tracts that influence postural muscle activity (Giovannucci et al., 2017; Ishikawa et al., 2009; McCall et al., 2017; Sawtell, 2010; Stein & Glickstein, 1986; Takakusaki, 2017). Previous work detected associations between ICP microstructure and proprioceptive-based balance performance (Gera et al., 2019), although it remains unclear if HC and PwMS possess differences in the degree of cerebellar contributions to proprioceptive-based balance control. PwMS have significantly delayed spinal conduction of proprioceptive information from the ankle joint (Cameron et al., 2008), a source of sensory input that provides the most salient information regarding postural sway (Fitzpatrick & Mccloskey, 1994), along with substantially degraded white matter microstructure of proprioceptive pathways conveying this information to the somatosensory cortex (Fling et al., 2014). Coupled with extensive thalamic atrophy found in PwMS early in the disease (Wylezinska et al., 2003), proprioceptive information may reach cortical areas too late to be useful in the maintenance of standing balance (Peterson DS, Gera G, Horak FB, 2016). Collectively, these results suggest that

the white matter microstructural integrity of the ICP contributes to proprioceptive-based balance performance in PwMS and that this may be to a greater degree than in HC.

To our knowledge, we are the first to examine associations between MCP microstructure and visual-based balance performance in PwMS. We report significant associations between both FA and RD of the MCP and visual-based balance performance, indicating that worse microstructure of the MCP is related to worse visual-based balance performance in PwMS. Visual-spatial information is processed in the primary visual cortex, relayed to the posterior parietal cortex (Stein et al., 1986) and ultimately reach deep cerebellar nuclei (Stein et al., 1992; Stoodley & Schmahmann, 2010; Buckner et al. 2011) via cortico-pontocerebellar projections through the MCP. The MCP delivers visual information to the fastigial nucleus (Kleine et al., 2003; Takakusaki, 2017; Zhang et al., 2016), which projects to both the vestibular and reticular nuclei to influence postural muscle activity via reticulospinal and vestibulospinal tracts (Abzug et al., 1974; Grillner & Hongo, 1972; McCall et al., 2017; Schepens & Drew, 2004). Previous work supporting the plausibility of associations between MCP structure and visual based balance performance found that stimulation of the vermis during eyes open, standing balance significantly improved postural stability (Ehsani et al., 2017), showcasing that when visual input is available, increased activity in the vermis (and subsequent alteration of fastigial nucleus activity) evokes substantial improvements in standing balance. Furthermore, Iu-Shiuan Lin and colleagues demonstrated that patients with impaired proprioception exhibited increased weighting of the visual and cerebellar systems during eyes open, standing balance (Lin et al., 2019), supporting our findings of a structure-function relationship between the microstructure of connections carrying visual

information to the cerebellum and balance performance when visual information is available and proprioceptive information is compromised.

Our findings of significant associations between ICP FA and RMS during vestibular-based balance in PwMS, not explored prior to this study, demonstrate that the structure of cerebellar connections carrying vestibular information are related to vestibular-based balance performance. The ICP carries vestibular information regarding head orientation to gravity to the fastigial nucleus (Angelaki & Cullen, 2008; Brooks & Cullen, 2009; C. Z. Martin et al., 2018) where it is then integrated with neck proprioceptive information to create a body-centered reference frame of gravity (Drijkoningen et al., 2015; Kleine et al., 2003; Shaikh et al., 2005; Voogd et al., 1996). The ICP sends body orientation information to postural control centers in the brainstem, such as the vestibular and reticular nuclei, to influence postural muscle tone and maintain standing balance (Chambers & Sprague, 1955; Re et al., 2017; Sprague & Chambers, 1953). This relationship has been demonstrated in human studies that found significant increases both in vestibular-mediated muscle reflex responsiveness in the soleus (Lam et al., 2017) and in postural sway after the depression of cerebellar activity during vestibular perturbation compared to conditions without altering cerebellar activity (Lam et al., 2016). This suggests cerebellar contributions to vestibular-mediated postural muscle reflexes and subsequently, postural sway during vestibular-based balance conditions. Similarly, Kammermeir et al. showed that patients with cerebellar impairment demonstrated abnormal postural responses when their vestibular systems were perturbed (Kammermeier et al., 2013). In addition, the association between ICP microstructure and vestibular-based balance performance was specific to RMS in PwMS. In recent work utilizing a comparable indicator of sway path variability, a significant reduction in

sway variability was found when cerebellar activity was increased during eyes closed standing balance with proprioceptive perturbations compared to no cerebellar stimulation (Poortvliet et al., 2018), proposing a relationship between increased cerebellar activity and improved standing balance performance in vestibular-based balance conditions.

We did not detect significant associations between SCP microstructure and balance performance in any sensory-manipulated condition, largely in agreement with previous work (Gera et al., 2019; Prosperini, Sbardella, et al., 2013). However, in the eyes open, firm surface condition (C1), Gera found significant associations between SCP RD and AP jerk, AP path length and AP frequency (Gera et al., 2019) while Prosperini found significant associations between SCP microstructure and CoP path length (Prosperini, Sbardella, et al., 2013). The SCP is comprised of projections from the interposed and dentate nuclei, which receive input from the intermediate zone and lateral zone of the cerebellum, respectively. While the intermediate zone is primarily implicated in upper extremity metering (Diener, Dichgans, Bacher, et al., 1984; Mauritz et al., 1979, 1981) and coordination of limb placement during locomotion (Arshavsky et al., 1972; Chambers et al., 1955; Udo et al., 1980), the lateral zone is involved with the timing, planning and coordination of complex movements (Hore et al., 1991; Manto, 2009; Schwartz et al., 1987). Previous work found that intermediate zone lesions resulted in standing balance oscillations solely in the AP direction (Diener, Dichgans, Hljlser, et al., 1984; Mauritz et al., 1979, 1981), thus, it is possible that we did not detect associations between SCP RD and balance performance in C1 because we did not examine AP components of our balance outcomes. Nevertheless, it is well-established that the importance of the intermediate and lateral zones to standing balance control is negligible (Chambers et al., 1955; Hore et al., 1991; Marsden, 2018; Morton et al., 2004; Thach et al., 1992)

compared to cerebellar regions that directly influence the fastigial nucleus (Diener, Dichgans, Bacher, et al., 1984; F. B. Horak et al., 1994; Scholz et al., 1986; Surgent et al., 2019; Takakusaki, 2017; Udo et al., 1980), therefore, our findings of associations between balance and microstructure of the ICP, MCP, but not SCP, are unsurprising.

6. CONCLUSION

Standing balance impairments in PwMS are well-documented, notably, in environmental conditions that remove or compromise available sensory inputs. In support of existing literature, we found impairments in both cerebellar peduncle white matter microstructure and standing balance performance in PwMS. We report that PwMS exhibited differentially worse vestibular-based balance performance than HC, detected by RMS, and that RMS in vestibular-based balance conditions was significantly related to ICP microstructure. Furthermore, PwMS demonstrated unique associations between both ICP microstructure and proprioceptive-based balance performance and MCP microstructure and visual-based balance performance that were not present in HC. Novel to our study, we found associations between both MCP microstructure and visual-based balance performance and ICP microstructure and vestibular-based balance performance. Our findings suggest that PwMS may place a greater reliance on cerebellar-regulated proprioceptive- and visual-based balance control and demonstrate worse vestibular-based balance than HC, augmenting previous work indicating abnormal vestibular-based balance and a contribution of the ICP to proprioceptive-based balance performance in PwMS. Future work investigating the influence of cerebellar functional activity on proprioceptive- and vestibular-based balance is needed to improve our understanding of the neural correlates of standing balance impairment in PwMS, and how the microstructural white matter alterations noted in the current study contribute to changes in intra- and inter- cerebellar functional communication.

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